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| EXAMINER | |
|---|---|
| CHEN, STACY BROWN | |
| ART UNIT | PAPER NUMBER |
| 1648 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/533,924 | AMARA ET AL. | |
| | Examiner | Art Unit | |
| | Stacy B. Chen | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *56-61 and 73-87* is/are pending in the application.

4a) Of the above claim(s) *78,79,82 and 83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-61,73-77,80,81 and 84-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/22/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. Applicant's amendment and remarks filed December 22, 2008 are acknowledged and entered. Claims 56-61 and new claims 73-87 are pending. Applicant's presentation of claims 78, 79, 82 and 83 introduce the effector molecule from West Nile virus. Previously, the claims were limited to the effector molecule of Dengue virus. The embodiments encompassing specifically West Nile (claims 78, 79, 82 and 83) are withdrawn from consideration, being drawn to a species that is independent or distinct from the invention originally claimed for the following reasons: while both West Nile virus and Dengue virus are Flaviviruses, they are distinct viruses comprised of different protein content and having different pathologies. Should the claims encompassing specifically Dengue virus (claim 76 at present) be found allowable, then the embodiment of West Nile virus will be rejoined. Since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 78, 79, 82 and 83 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Claims 56-61, 73-77, 80, 81 and 84-87 are under examination.

***Response to Amendment***

2. The following objection(s) and rejection(s) are withdrawn:

- The objection to claims 56-61 with regard to the recitation of dendritic cells, is withdrawn in view of Applicant's amendment.
- The rejection of claims 56-61 under 35 U.S.C. 112, second paragraph, with particular regard to the Office's previous assertion that the binding values were not adequately defined, is withdrawn in view of Applicant's persuasive arguments.

***Specification***

3. The specification remains objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 56 recites "about 95% modulation of binding of the viral effector molecule to dendritic cells by the test substance". The specification discloses 95% inhibition in paragraph [0109], but not 95% modulation, which encompasses more than inhibition activity.

Applicant's arguments have been carefully considered but fail to persuade. Applicant asserts that MPEP 608.01(o) and 37 C.F.R. 1.75(d)(1) are not relevant to claim 56 because it was an original claim, not one added late in prosecution. 37 C.F.R. 1.75(d)(1) states:

> The claim or claims must conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description.

37 C.F.R. 1.75(d)(1) does not distinguish between original claims and claims added late in prosecution (which is addressed in MPEP 608.01(o). Therefore, Applicant is required to amend the specification to provide proper antecedent basis for the subject matter of claim 65.

***Claims Summary***

4. The claims as amended are drawn to a method of identifying a DC-SIGN modulator, or more specifically, a DC-SIGN blocker. (DC-SIGN is a dendritic cell-specific adhesion receptor, also called ICAM-grabbing non integrin and CD-209. DC-SIGN is the ligand of ICAM-3, see specification page 5, paragraph [013]). The specification defines "DC-SIGN receptor" as DC-SIGN, DC-SIGNR (DC-SIGN related protein), or homologues thereof (page 17, paragraph [057]). The method steps comprise the determination of a test substance binding

modulation/inhibition value. This value is determined by dividing a test substance binding value by a baseline binding value for a viral effector molecule binding moiety (*i.e.*, flavivirus effector molecule such as Dengue envelope glycoprotein or West Nile envelope glycoprotein).

**Test substance binding inhibition value = test substance binding value / baseline binding value**

The *test substance binding value* is determined by exposing cultured cells comprising a DC-SIGN receptor to a marked viral effector molecule binding moiety in the presence of a test substance, and allowing binding equilibrium to be reached. The extent of binding is the test substance binding value. The *baseline binding value* is determined by exposing cultured cells comprising a DC-SIGN receptor to a marked viral effector molecule binding moiety and allowing binding equilibrium to be reached. The extent of binding is the baseline binding value. If the test substance binding inhibition value represents an about 95% modulation or inhibition of binding of the viral effector molecule to dendritic cells by a test substance, the test substance is deemed a substance that substantially modulates or inhibits the binding of a viral effector molecule to the DC-SIGN receptor.

Specifically, the cells are dendritic cells (DC), or human acute monocytic leukemia cells (THP-1, ATCC TIB 202), or THP-1Δ35 cells (35 amino acid truncation including both the dileucine motif and the tyrosine-based motif).

### *Claim Rejections - 35 USC § 112*

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 56-61, 73-77, 80 and 81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

All claims refer to "DC-SIGN receptor". As noted above, the specification defines "DC-SIGN receptor" in the human context, as DC-SIGN, DC-SIGNR (DC-SIGN related protein), or homologues thereof [page 17, paragraph [057]). The "DC-SIGN receptor" in the non-human animals refers to homologues of a human DC-SIGN receptor (page 17, paragraph [058]. While the identity of DC-SIGN and DC-SIGNR is recognized in the art, **the homologues of DC-SIGN and DC-SIGNR are not clearly defined in the specification**. Homologues broadly encompass any protein having some degree of similarity (structurally or functionally) to DC-SIGN and DC-SIGNR. Further, according to paragraph [058], the receptor may be a homolog of a homolog. Applicant has not defined the homologues' structures such that the metes and bounds of the homologues can be determined.

Applicant's arguments have been carefully considered but fail to persuade. Applicant presents evidence in support of the definite identity of DC-SIGN and DC-SIGNR. The Office has already acknowledged that the identities of these two molecules are readily discernable in the art. The problem that the Office is addressing is the lack of definiteness for homologues of DC-SIGN and homologues of DC-SIGNR, and homologues of homologues, which are embodiments encompassed within the term "DC-SIGN receptor", as explained above and outlined in the specification (page 17, paragraph [057]). Applicant has not addressed this aspect of indefiniteness with regard to the homologues. Therefore, the rejection is maintained for reasons of record.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56-61, 73-77, 80 and 81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a DC-SIGN modulator/blocker, wherein the method employs a DC-SIGN receptor that is DC-SIGN or DC-SIGNR, does not does not reasonably provide enablement for a method that employs homologues of DC-SIGN, homologues of DC-SIGNR, or homologues of homologues. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims encompass a method of identifying a DC-SIGN modulator that modulates the binding of a marked viral effector molecule to DC-SIGN. As discussed in the rejection under 35 U.S.C. 112, second paragraph above, the definition of DC-SIGN is not clear because it encompasses homologues of both DC-SIGN, DC-SIGNR and homologues of homologues.

The state of the art confirms that DC-SIGN mediates Dengue virus infection of human dendritic cells, specifically THP-1 cells, by binding envelope protein (Tassaneetrithep *et al.*, *The Journal of Experimental Medicine*, 2003, 197(7):823-829, see abstract and page 828, first column, filed in IDS of 5/4/05). The state of the art also confirms that DC-SIGN binds Human Cytomegalovirus (envelope protein B) and HIV gp120 (Kwon *et al.*, *Immunity*, 2002, 16(1):135-144, abstract, filed in IDS of 5/4/05, and Halary *et al.*, *Immunity*, 17(5):653-664, abstract, filed in IDS of 5/4/05).

The specification does not provide sufficient guidance for identifying DC-SIGN homologues, DC-SIGNR homologues, or homologues of homologues. There is insufficient information relating to the construction of homologues that would be useful in the claimed method.

Given the breadth of the claims, the state of the art, and the limited guidance and working examples in the specification, it would require undue experimentation to practice the claimed method in its full breadth.

Applicant's arguments have been carefully considered but fail to persuade. Applicant argues that since the sequences of DC-SIGN and DC-SIGNR are known, and conserved domains of both molecules are known, the skilled artisan could examine the interaction between the DC-SIGN homologues and a variety of known molecules known to interact with DC-SIGN.

In response to Applicant's argument, the Office has considered Pöhlman *et al.* (*PNAS USA* 98:2670-2675, 2001, "Pöhlman") which discloses that DC-SIGN and DC-SIGNR share 77% amino acid identity and a C-type lectin domain. Pöhlman's disclosure is not sufficient to provide one of skill in the art with enough information to be able to make homologues of DC-SIGN, aside from DC-SIGNR. It remains unclear how one would be able to make homologues of DC-SIGN without undue experimentation. The specification does not disclose the retention of any particular structure. Although Pöhlman discloses that the C-type lectin domain is shared between DC-SIGN and DC-SIGNR, it is not a complete match. Unless the specification were to define homologues as retaining the C-type lectin domain of the original DC-SIGN, one would not know where to make modifications to create homologues of DC-SIGN. Even in those molecules that retain a C-type lectin domain, one would not know how to modify that region and

still retain function. While it is possible to make and test thousands of potential homologues of DC-SIGN and DC-SIGNR, and homologues of homologues, it would require undue experimentation due to the lack of information in the specification regarding the construction of homologues with DC-SIGN function. Therefore, the rejection is maintained.

7. (*New Rejection*) Claims 75 and 80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that THP-1Δ35 cells are required to practice the claimed invention because they are a necessary limitation for the success of the invention as stated in the claims. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the cells. See 37 CFR 1.802. One cannot practice the claimed invention without the exact cells being claimed because Applicant is requiring the use of a specific cell line. While it is possible to make one that is similar to THP-1Δ35 cells, the claim requires the THP-1Δ35 cell. Therefore, access to THP-1Δ35 cells is required to practice the invention. The specification does not provide a repeatable method for obtaining THP-1Δ35 cells without access to the cells and they do not appear to be readily available material.

Deposit of THP-1Δ35 cells in a recognized deposit facility would satisfy the enablement requirements of 35 U.S.C. 112, because the strains would be readily available to the public to practice the invention claimed, see 37 CFR 1.801- 37 CFR 1.809.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;
(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;
(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and
(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 56-58, 73, 84 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Figdor *et al.* (WO 00/63251, "Figdor", filed in IDS of 5/4/05). The claims are summarized above. Figdor discloses the identification of a compound that binds to DC-SIGN on dendritic cells ("a C-type lectin") for modulating the interaction, particularly, reducing the interaction (see page 6, first and second full paragraphs). Figdor discloses the determination of antibodies that bind to DC-SIGN on dendritic cells, and the determination that those antibodies can reduce HIV infectivity of dendritic cells (see Example 8). Although the specific method steps of determining baseline values are not explicitly set forth in Figdor's disclosure, the basic steps are disclosed:

- Dendritic cells expressing DC-SIGN are pulsed with HIV-1 and infection is measured. This qualifies as a baseline binding value.
- Dendritic cells are also pulsed with anti-DC-SIGN antibodies prior to exposure to HIV-infected PBMCs, and infection is measured. This qualifies as a binding value in the presence of a test substance.
- A comparison between the two values is determined (see pages 28-29).

It would have been well within the ability of the ordinary artisan to select a value (a percentage, for example) that represents significant modulation of DC-SIGN activity. Therefore, the claims would have been obvious in view of the disclosure of Figdor.

Applicant's arguments have been carefully considered but fail to persuade. Applicant argues that the Office does not provide a reason why one would modify Figdor's disclosure to include the process of determining a baseline binding value, determining a binding value in the presence of a test substance and determining a test substance binding modulation value for the test substance.

In view of the rejection outlined above, it is important to note that the respective binding values are determined in Figdor although the same words are not used (*i.e.,* "binding values"). What is lacking is the step of *dividing* the binding value for the viral effector molecule binding moiety in the presence of the test substance by the baseline binding value. However, it would have been obvious to derive a number to represent the comparison between the two values measured by Figdor. Note that Figdor does compare the two values and uses that comparison as a basis for determining whether an antibody reducing HIV infectivity of dendritic cells. Therefore, the rejection is maintained for reasons of record.

9. (*New Rejection*) Claims 85 and 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Figdor, as applied to claims 56 and 57 above, and further in view of Pöhlman *et al.* (*PNAS USA* 98:2670-2675, 2001, "Pöhlman"). Figdor discloses the determination of antibodies that bind to DC-SIGN on dendritic cells, and the determination that those antibodies

can reduce HIV infectivity of dendritic cells (see Example 8). Figdor does not suggest the use of DC-SIGNR by expressing DC-SIGNR on dendritic cells.

However, it would have been obvious to perform the same assay taught by Figdor using cells that express DC-SIGNR. Pöhlman discloses that DC-SIGN and DC-SIGNR share 77% amino acid identity and a C-type lectin domain; also taught is that DC-SIGNR is expressed on endothelial cells and binds to human and simian immunodeficiency viruses and activates infection in trans (see abstract and page 2670, second column, first paragraph). One would have been motivated to use DC-SIGNR because it is a known homolog of DC-SIGN. By performing the assay with DC-SIGN's homolog, DC-SIGNR, one would have been able to identify antibodies that are capable of binding DC-SIGNR, which could then been determined to be capable of reducing HIV infectivity. By identifying antibodies that bind DC-SIGNR in addition to those that bind DC-SIGN, one would have had a more comprehensive repertory of antibodies with which to inhibit HIV infectivity. One would have had a reasonable expectation of success that Figdor's assay would have identified antibodies that bind DC-SIGNR because of the well known art of antibody binding assays.

10. Claims 59 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Figdor *et al.* (WO 00/63251, "Figdor", filed in IDS of 5/4/05) as applied to claims 56 and 57 above, and further in view of Banka *et al.* (*Journal of Lipid Research*, 1991, 32:35-43, "Banka"). The claims are limited to THP-1 cells, which are human acute monocytic leukemia cells. Figdor does not disclose THP-1 dendritic cells, although Figdor does disclose the derivation of DCs from monocytes (see Example 1). It is well known in the art, evidenced by Figdor, that DCs are

derived from monocytes. Given that Figdor uses cells that express DC-SIGN, and the THP-1 monocytic cell line is immortalized and produces immature DCs, it would have been obvious to select a cell line like THP-1 for an assay that requires continuous expression of DC-SIGN because the THP-1 cell line is expected to produce dendritic cells that express DC-SIGN. One would have had a reasonable expectation of success that the THP-1 cell line would have expressed DC-SIGN because it produces dendritic cells, which are known to express DC-SIGN.

***Conclusion***

11. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30), alternate Fridays off,. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B Chen/
Primary Examiner, Art Unit 1648